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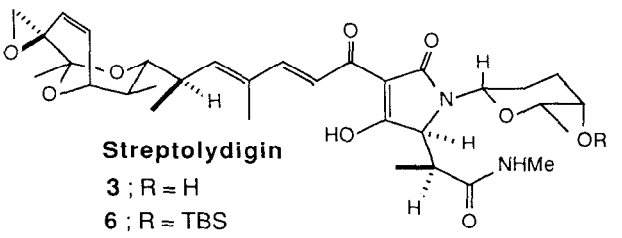
A NON-CONGENER BASED SYNTHESIS OF L-(-)-RHODINOSE AND OF A C_4 HYDROXYL PROTECTED DERIVATIVE

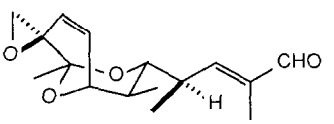
Richard H. Schlessinger* and Deborah D. Graves[1]
Department of Chemistry
University of Rochester
Rochester, New York 14627

Summary: *A practical five step construction of the L-(-)-rhodinose derivative **1** and of L-(-)-rhodinose (**2**) from O-benzyl (S)-ethyl lactate is described. Optical rotations and other data for both **1** and **2** as well as for intermediates leading to them are provided.*

As part of an effort to construct the antibiotic streptolydigin (**3**),[2] a practical means of securing



Streptolydigin
3 ; R = H
6 ; R = TBS



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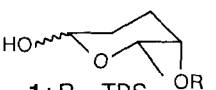
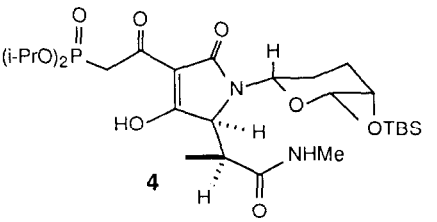


1 ; R = TBS
2 ; R = H



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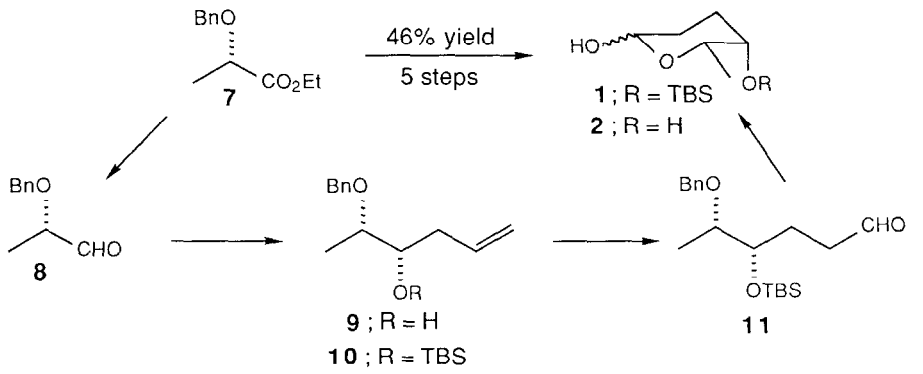
quantities of the C-4 hydroxyl protected derivative **1** of L-(-)-rhodinose (**2**) was required.[3] Our intention was to incorporate **1** into a 3-acyltetramic acid to formulate the Emmons reagent **4** for olefination with the unsaturated aldehyde **5** to obtain the streptolydigin derivative **6**.[4] The parent sugar, **2**, exists and could react as a mixture of furanose and pyranose species.[5] Hence, it was clear that a C-4 hydroxyl protected form of **2** was required. In this context, we chose to prepare the

t-butyldimethylsilyl (TBS) derivative **1** with the hope that the TBS group could be cleaved under sufficiently mild conditions so as not to perturb the rather fragile functional groups arrayed in the system depicted as **6**. At the time we started this problem, the literature revealed multistep preparations of **2** from sugars,[6] and three syntheses from non-congener sources, one racemic,[7] and the other two starting from optically active substances.[8] For a variety of reasons, none of these routes appealed to us as a means of preparing **1**.[9]

We commenced our preparation of **1** from O-benzyl (S)-ethyl lactate (**7**)[10] $[\alpha]_D$ -82.7° (c 3.1, $CHCl_3$) which was reduced in CH_2Cl_2 solution (0.25 M) with diisobutylaluminum hydride (1.2 eq, Aldrich, 1.0 M in hexanes) at -78°C. The resulting unstable aldehyde **8** was then immediately condensed under chelation controlled conditions[11] with tri-*n*-butylallylstannane (1.2 eq) in the presence of $MgBr_2 \cdot Et_2O$ (1.2 eq, Aldrich) in CH_2Cl_2 solution (0.2 M, -45°C, 12 h) to afford, after chromatography, the alcohol **9** as a single isomer $[\alpha]_D$ +52.2° (c 2.6, CH_2Cl_2) in 85% yield from the ester **7**.[12] The alcohol portion of **9** (1.0 eq) was then reacted with *t*-butyldimethylsilyl triflate (TBSOTf, 1.5 eq) in CH_2Cl_2 (0.33 M) containing 2,6-lutidine (2.0 eq) for 45 min at 22°C to give **10** $[\alpha]_D$ +2.5° (c 2.98, CH_2Cl_2) in 98% yield.

Hydroboration-oxidation of the olefinic residue of **10** to the aldehyde **11** was then carried out under the following conditions[13] which proved considerably superior with respect to both yield and purity to a number of variants of this reaction that were examined. Thus, **10** (1 eq) in CH_2Cl_2 (0.33 M, 22°C) was treated with solid 9-BBN dimer (1.6 eq, Alfa), and after stirring for 30 min, the mixture was refluxed for 1.75 h. Upon cooling to 22°C, the reaction was delivered, *via* cannula, to a solution of CH_2Cl_2 (-40°C) containing PCC (12.0 eq, 1.33 M). After stirring at -40°C for 30 min, the oxidizing mixture was progressively warmed to 0°C, 30 min; 22°C, 30 min; reflux 2.5 h; and 22°C, 2.5 h. Standard workup and filtration chromatography on silica gel afforded **11** $[\alpha]_D$ -8.7° (c 2.08, CH_2Cl_2) in 61% yield. Finally, debenzylation of **11** in THF solution (0.2 M, base-washed glassware) in the presence of palladium (10% on charcoal) under 1.5 atm of hydrogen for 8 h at 22°C gave **1** $[\alpha]_D$ -14.6° (c 2.40, CH_2Cl_2), mp 71-72°C after sublimation, as a mixture of anomers in 91% yield, 46% overall yield in five steps from the ester **7**.[14] L-(-)-rhodinose (**2**), $[\alpha]_D$ -8.03° (c 1.42, acetone),[15] was obtained from **1** (1.0 eq) in 89% yield by treatment of the latter in THF solution (0.23 M) with *n*-Bu_4NF (2.0 eq, Aldrich) at 0°C to 22°C for 7 h followed by addition of water and continuous extraction with CH_2Cl_2 and flash chromatography on silica gel.[16]



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14. Compound **1** (anomeric mixture): IR ($CHCl_3$) 3592, 3405 (broad), 2952, 2930, 2889, 2855, 1460, 1445, 1252, 1125, 1070, 1044, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (1.4:1 mixture of α and ß anomers, respectively) δ 5.32 (br s, 1H, α anomer), 4.75 (t, J=9 Hz, 1 H, ß anomer–collapses to d when D_2O is added), 4.11 (q, J=7 Hz, 1H, α anomer–collapses to d when D_2O is added), 3.62 (m, 1H, α anomer and 1H, ß anomer), 3.51 (br s, 1H, ß anomer. 3.02 (d) and 2.59 (s) (OH, both anomers), 2.08–1.49 (complex m, 4H, both anomers), 1.22 (t, J=7 Hz, 3H, ß anomer), 1.14 (t, J=7 Hz, 3H, α anomer), 0.94 (s, 9H, both anomers), 0.09 (s, 6H, both anomers); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 96.46, 91.58, 74.73, 68.18, 67.28, 67.09, 31.61, 30.51, 27.58, 26.19, 25.95, 25.69, 24.14, 18.25, 17.81, 17.51, 14.09, -4.54, -4.21; MS, *m/e* (relative intensity): 230 (0.6), 229 (M^+ -17, 3.7), 201 (13.3), 171 (38.5), 145 (15.6), 131 (13.5), 101 (22.6), 97 (14.0), 75 (100.0), 73 (71.1), 69 (13.6), 59 (16.9), 43 (37.8).
15. Rhodinose (**2**) is reported to have an $[\alpha]_D$ -11.0° (acetone, no concentration given) reference 2. Literature rotations for synthetic rhodinose range from -6.7° to -9.0° (reference 8b and references cited therein). In view of the variation in rotation values for **2**, we undertook to evaluate the optical purity of **9** by ^1H NMR. Treatment of **9** with *d*-10-camphorsulfonyl chloride in pyridine gave in excellent yield the corresponding ester. ^1H NMR examination of the crude reaction product (400 MHz, $CDCl_3$) showed no perceptible amount of a diastereomer. The starting material, S-ethyl lactate, was examined in the same manner and found to be optically pure. Since the chemical transformation of **9** into rhodinose (**2**) does not involve either stereogenic center present in **9**, we feel confident that synthetic **2** prepared in the fashion described is optically pure.
16. Compound **2** (anomeric mixtures of pyranose and furanose forms): IR ($CHCl_3$) 3597, 3406 (broad), 2980, 2935, 1450, 1380, 1243, 1062, 1019 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), equilibrated 2 h prior to recording the spectrum. The ratios of α and ß anomers, and of pyranose and furanose forms, are both solvent and concentration dependent, δ 5.58 (poorly defined d), 5.51 (br s), 5.29 (br s), 4.76 (poorly defined t) (altogether 1H), 4.50 (br s, exchangeable with D_2O), 4.22 (q, J=7 Hz), 4.03 (q, J=7 Hz), 3.91 (q, J=7 Hz), 3.68 (q, J=7 Hz), 3.60 (t, J=7 Hz), 3.48 (br s), 3.40 (br s, exchangeable with D_2O), 2.98 (m), 2.88 (br s, diminishable with D_2O), 2.63 (s), 2.34 (br s, exchangeable with D_2O), 2.18 (s) (4.50–2.18 inclusive 4H), 2.10–1.50 (complex m, 4H), 1.30–1.12 (complex m, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$, equilibrated for 1.2 h before the spectrum was recorded) δ 98.83, 98.28, 96.46, 91.67, 84.98, 82.98, 74.29, 70.69, 70.37, 67.48, 66.52, 66.35, 34.07, 33.33, 29.80, 29.34, 27.02, 26.11, 25.43, 23.71, 19.74, 19.16, 17.25, 17.19; MS, *m/e* (relative intensity): 116 (1.6), 115 (M^+ -17, 14.9), 114 (3.5), 103 (10.6), 88 (19.2), 87 (61.0), 75 (14.2), 71 (18.6), 69 (40.4), 58 (31.5), 57 (36.9), 45 (100.0), 44 (55.5), 43 (61.8), 41 (58.8), 31 (32.8).

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